Helms
147346

=> fil reg;s gonadotropin releasing hormone?/cn

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.45	0.45

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L1 4 GONADOTROPIN RELEASING HORMONE?/CN

=> fil medl,caplus,biosis,embase,wpids;s (l1 or gonadotropin releas? hormone?)(l)(adenocarcinoma or benign uterine or lyomoma or endometria? island or pituitary (w)(tumour or tumor)(w)adenoma)

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.20	4.65

FILE 'MEDLINE' ENTERED AT 15:03:39 ON 29 MAR 2000

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L2 25 FILE MEDLINE
L3 15 FILE CAPLUS
L4 25 FILE BIOSIS
L5 26 FILE EMBASE
L6 3 FILE WPIDS

TOTAL FOR ALL FILES
L7 94 (L1 OR GONADOTROPIN RELEAS? HORMONE?)(L)(ADENOCARCINOMA OR BENIG
N UTERINE OR LYOMOMA OR ENDOMETRIA? ISLAND OR PITUITARY
(W)(TUMO

UR OR TUMOR)(W) ADENOMA)

=> s l7 and (pseudomon? exotoxin or exotoxin)

L8 2 FILE MEDLINE
L9 3 FILE CAPLUS
L10 2 FILE BIOSIS
L11 2 FILE EMBASE
L12 1 FILE WPIDS

TOTAL FOR ALL FILES
L13 10 L7 AND (PSEUDOMON? EXOTOXIN OR EXOTOXIN)

=> dup rem l13

PROCESSING COMPLETED FOR L13
L14 4 DUP REM L13 (6 DUPLICATES REMOVED)

=> d cbib abs 1-4

L14 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
1999:626350 Document No. 131:253318 Methods of adenocarcinoma cancer diagnosis using a chimeric toxin of Pseudomonas. Lorberboum-Galski, Haya;
Ben-Yehudah, Ami; Nechushtan, Amotz; Yarkoni, Shai; Marianovsky, Irina (Yissum Research Development Company of the Hebrew University of Jerusalem, Israel). PCT Int. Appl. WO 9949059 A2 19990930, 45 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH,
CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IL166 19990324. PRIORITY: US 1998-46992 19980324.
AB The present invention relates to methods for cancer diagnosis using a chimeric toxin. In particular, the invention relates to the use of a chimeric toxin composed of **gonadotropin releasing hormone** (GnRH) and **Pseudomonas exotoxin** A (PE) to detect a tumor-assocd. epitope expressed by human **adenocarcinomas**. Mutated GnRH-PE mols. that bind but do not kill tumor cells are exemplified.

L14 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
1999310314 Document Number: 99310314. Linker-based GnRH-PE chimeric proteins
inhibit cancer growth in nude mice. Ben-Yehudah A; Yarkoni S; Nechushtan A; Belostotsky R; Lorberboum-Galski H. (Department of Cellular Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem, Israel.) MEDICAL ONCOLOGY, (1999 Apr) 16 (1) 38-45. Journal code: B3A. ISSN: 1357-0560. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Since the number of cancer-related deaths has not decreased in recent years, major efforts are being made to find new drugs for cancer treatment. In this report we introduce the **gonadotropin releasing hormone-Pseudomonas exotoxin** (GnRH-PE) based chimeric proteins L-GnRH-PE66 and L-GnRH-PE40. These proteins are composed of a GnRH moiety attached to modified forms of

Pseudomonas exotoxin via a polylinker (gly4ser)2. The chimeric proteins L-GnRH-PE66 and L-GnRH-PE40 have the ability to target and kill **adenocarcinoma** cell lines in vitro, whereas non-**adenocarcinoma** cell lines are not affected. We demonstrate that L-GnRH-PE66 and L-GnRH-PE40 efficiently inhibit cancer growth. Nude mice were injected subcutaneously with the SW-48 **adenocarcinoma** cell line to produce xenograft tumours. When the tumours were established and visible, the animals were injected with chimeric proteins for 10 days. At the end of this period, a reduction of up to 3-fold in tumor size was obtained in the treated mice, as compared with the control group, which received equivalent amounts of GnRH; the difference was even greater 13 days after termination of treatment. Thus, the chimeric proteins L-GnRH-PE66 and L-GnRH-PE40 are promising candidates for treatment of a variety of **adenocarcinomas** and their use in humans should be considered.

L14 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2000 ACS
1998:1391 Document No. 128:84392 Chimeric toxins for targeted cancer therapy. Yarkoni, Shai; Nechushtan, Amotz; Lorberboum-Galski, Haya; Marianovski, Irina (Yissum Research Development Company, Israel; Yarkoni, Shai; Nechushtan, Amotz; Lorberboum-Galski, Haya; Marianovski, Irina). PCT Int. Appl. WO 9746259 A2 19971211, 30 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-IL180 19970604. PRIORITY: IL 1996-118570 19960604.

AB Chimeric toxins targeted to neoplastic cells comprise cell-targeting moieties and cell-killing moieties for recognizing and destroying the neoplastic cells, resp., wherein the cell-targeting moieties consist of **gonadotropin-releasing hormone** homologs and the cell-killing moieties consist of **Pseudomonas exotoxin** A. The chimeric toxins are useful in cancer therapy for treating malignant carcinoma cells and benign hyperplasia, including uterine leiomyoma cells, extrauterine **endometrial island** cells, benign hyperplasia of the prostate, and breast and **pituitary tumor adenoma** cells. Thus, a 36-bp synthetic oligonucleotide consisting of the **gonadotropin-releasing hormone** coding sequence with a Gly6.fwdarw.Trp replacement, flanked by NdeI and HindIII restriction sites, was inserted into plasmid pJY3A1136-1,3 carrying a mutated **Pseudomonas exotoxin** A gene. The chimeric protein was expressed in Escherichia coli BL21 carrying the plasmid after induction with iso-Pr D-thiogalactoside. The expressed protein was cytotoxic to SW-48 colon carcinoma cells and HepG2 hepatocarcinoma cells at 0.3 .mu.g total protein (E. coli insol. fraction enriched with chimeric protein) per microplate well.

L14 ANSWER 4 OF 4 MEDLINE DUPLICATE 3
97269076 Document Number: 97269076. **Adenocarcinoma** cells are targeted by the new GnRH-PE66 chimeric toxin through specific **gonadotropin-releasing hormone** binding sites. Nechushtan A; Yarkoni S; Marianovsky I; Lorberboum-Galski H. (Department of Cellular Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem 91120, Israel.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Apr 25) 272 (17) 11597-603. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Luteinizing hormone-releasing hormone, also termed **gonadotropin-**

releasing hormone (GnRH), accounts for the hypothalamic-pituitary gonadal control of human reproduction. The involvement of GnRH has been demonstrated in several carcinomas of hormone-responsive tissues. Exploiting this common feature, we constructed a **Pseudomonas exotoxin** (PE)-based chimeric toxin (GnRH-PE66) aimed at targeting those cancer cells bearing GnRH binding sites. We report here the strong growth inhibition and killing of a surprisingly wide variety of cancers, confined to the **adenocarcinoma** type. These cancer cells arising from hormone-responsive tissues, as well as non-responsive ones, express specific GnRH binding sites as indicated by the marked killing of ovarian, breast, endometrial, cervical, colon, lung, hepatic, and renal **adenocarcinoma**. This cytotoxicity is specific as it could be blocked upon addition of excess GnRH. The specificity of GnRH-PE66 chimeric toxin was also confirmed by GnRH binding assays, and its ability to prevent the formation of colon cancer xenografts in nude mice is presented. Although the functional role of specific GnRH binding sites in human carcinomas remains obscure, GnRH-PE66 displays considerable targeting potential and its use as a therapeutic agent for cancer should be considered.

```
=> s (l1 or gonadotropin releas? hormone? or gnrh)(2a)pe66

L15           2 FILE MEDLINE
L16           1 FILE CAPLUS
L17           1 FILE BIOSIS
L18           2 FILE EMBASE
L19           0 FILE WPIDS

TOTAL FOR ALL FILES
L20           6 (L1 OR GONADOTROPIN RELEAS? HORMONE? OR GNRH)(2A) PE66

=> s l20 not l13

L21           0 FILE MEDLINE
L22           0 FILE CAPLUS
L23           0 FILE BIOSIS
L24           0 FILE EMBASE
L25           0 FILE WPIDS

TOTAL FOR ALL FILES
L26           0 L20 NOT L13

=> s cancer and toxin and (l1 or gonadotropin releas? hormone? or gnrh)

L27           2 FILE MEDLINE
L28           7 FILE CAPLUS
L29           6 FILE BIOSIS
L30           3 FILE EMBASE
L31           6 FILE WPIDS

TOTAL FOR ALL FILES
L32          24 CANCER AND TOXIN AND (L1 OR GONADOTROPIN RELEAS? HORMONE? OR
                GNRH)

=> s l32 not (l20 or l13)

L33           1 FILE MEDLINE
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L34 4 FILE CAPLUS
L35 5 FILE BIOSIS
L36 2 FILE EMBASE
L37 5 FILE WPIDS

TOTAL FOR ALL FILES
L38 17 L32 NOT (L20 OR L13)

=> dup rem l38

PROCESSING COMPLETED FOR L38
L39 13 DUP REM L38 (4 DUPLICATES REMOVED)

=> d 1-13 cbib abs;s yarkoni s?/au,in;s nechushtan a?/au,in

L39 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2000 ACS
1999:693563 Document No. 132:602 The luteinizing hormone-releasing hormone receptor in human prostate **cancer** cells: messenger ribonucleic acid expression, molecular size, and signal transduction pathway.
Limonta, Patrizia; Moretti, Roberta M.; Marelli, Marina Montagnani; Dondi, Donatella; Parenti, Marco; Motta, Marcella (Center for Endocrinological Oncology, Department of Endocrinology, University of Milano, Milan, 20133, Italy). Endocrinology, 140(11), 5250-5256 (English) 1999. CODEN: ENDOAO.
ISSN: 0013-7227. Publisher: Endocrine Society.
AB Evidence has accumulated indicating that LHRH might behave as an autocrine/paracrine growth inhibitory factor in some peripheral tumors. However, LHRH receptors in tumor cells have not been fully characterized, so far. The present expts. were performed to analyze: (1) the mRNA expression; (2) the mol. size; and (3) the signal transduction pathway of LHRH receptors in prostate **cancer**. For these studies, the human androgen-dependent LNCaP and androgen-independent DU 145 prostate **cancer** cell lines were used. (1) By RT-PCR, a complementary DNA product which hybridized with a 32P-labeled oligonucleotide probe specific for the pituitary LHRH receptor complementary DNA, was found both in LNCaP and in DU 145 cells. (2) Western blot anal., using a monoclonal antibody raised against the human pituitary LHRH receptor, revealed the presence of a protein band of approx. 64 kDa (corresponding to the mol. mass of the pituitary receptor) in both cell lines. (3) In LNCaP and DU 145 cells, pertussis **toxin** completely abrogated the antiproliferative action of a LHRH agonist (LHRH-A). Moreover, LHRH-A substantially antagonized the pertussis **toxin**-catalyzed ADP-ribosylation of a G.alpha.i protein. Finally, LHRH-A significantly counteracted the forskolin-induced increase of intracellular cAMP levels in both cell lines. These data demonstrate that the LHRH receptor, which is present in prostate **cancer** cells, independently of whether they are androgen-dependent or not, corresponds to the pituitary receptor, in terms of mRNA expression and protein mol. size. However, at variance with the receptor of the gonadotrophs, prostate **cancer** LHRH receptor seems to be coupled to the G.alpha.i protein-cAMP signal transduction pathway, rather than to the G.alpha.q/11-phospholipase C signaling system.
This might be responsible for the different actions of LHRH in anterior

pituitary and in prostate **cancer**.

L39 ANSWER 2 OF 13 MEDLINE DUPLICATE 1
2000005680 Document Number: 20005680. Role of mitogen-activated protein kinase/extracellular signal-regulated kinase cascade in **gonadotropin-releasing hormone**-induced growth inhibition of a human ovarian **cancer** cell line. Kimura A; Ohmichi M; Kurachi H; Ikegami H; Hayakawa J; Tasaka K; Kanda Y; Nishio Y; Jikihara H; Matsuura N; Murata Y. (Department of Obstetrics and Gynecology, Osaka University Medical School, Suita, Japan.) CANCER RESEARCH, (1999 Oct 15) 59 (20) 5133-42. Journal code: CNF. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Although **gonadotropin-releasing hormone** agonists (GnRHa) have been used in the therapy of the endocrine-dependent **cancers**, their biological mechanism remained obscure. We have studied the roles of mitogen-activated protein kinase family in the antiproliferative effect of GnRHa on the Caov-3 human ovarian **cancer** cell line. Reverse transcription-PCR assays confirmed mRNA for **GnRH** receptor in Caov-3 cells. In the presence of 1 microM GnRHa, the proliferation of cells was significantly reduced to 76% of controls after 24 h, and the effect was sustained up to 4 days. Although GnRHa had no effect on the activation of the Jun N-terminal kinase (JNK), treatment of Caov-3 cells with GnRHa activated extracellular signal-regulated protein kinase (ERK), and its effect was more than that induced by **GnRH**. Activation of ERK by GnRHa occurred within 5 min, with the maximum occurring at 3 h and sustained until 24 h. GnRHa also activated ERK kinase (mitogen-activated protein/ERK kinase) and resulted in an increase in phosphorylation of son of sevenless (Sos), and Shc. Furthermore, we examined the mechanism by which GnRHa induced ERK activation. Both pertussis **toxin** (10 ng/ml), which inactivates Gi/Go proteins, and expression of a peptide derived from the carboxyl terminus of the beta-adrenergic receptor kinase I, which specifically blocks signaling mediated by the betagamma subunits of G proteins, blocked the GnRHa-induced ERK activation. Phorbol 12-myristate 13-acetate (PMA) also induced the ERK activity, but pretreatment of the cultured cells with PMA to down-regulate protein kinase C did not abolish the activation of ERK by GnRHa. Elimination of extracellular Ca2+ by EGTA also did not abolish the activation of ERK by GnRHa. To examine the role of ERK cascade in the antiproliferative effect of GnRHa, PD98059, an inhibitor of mitogen-activated protein/ERK kinase, was used. This inhibitor canceled the antiproliferative effect of GnRHa and apparently reversed the **GnRH**-induced dephosphorylation of the retinoblastoma protein, the hyperphosphorylation of which is a hallmark of G1-S transition in the cell cycle. These results provide evidence that GnRHa stimulation of ERK activity may be mediated by Gbetagamma protein, not by PMA-sensitive protein kinase C nor extracellular Ca2+ in the Caov-3 human ovarian **cancer** cell line, suggesting that this cascade may play an important role in the antiproliferative effect of GnRHa.

L39 ANSWER 3 OF 13 BIOSIS COPYRIGHT 2000 BIOSIS
2000:62857 Document No.: PREV200000062857. Effect of GHRH and peptides from the vasoactive intestinal peptide family on cAMP production of human **cancer** cell lines in vitro. Csernus, V.; Schally, A. V. (1); Groot, K.. (1) Endocrine, Polypeptide and Cancer Institute, Veteran Affairs Medical Center, 1601 Perdido Street, New Orleans, LA USA. Journal of Endocrinology, (Nov., 1999) Vol. 163, No. 2, pp. 269-280. ISSN: 0022-0795. Language: English. Summary Language: English.

AB Antagonistic analogs of GHRH inhibit growth of various human **cancers** both in vivo and in vitro. To elucidate the mechanism of direct action of the antagonistic analogs of GHRH on tumor cells, cultured human **cancer** cells were exposed to GHRH, vasoactive intestinal peptide (VIP), secretin, glucagon, neuropeptide-Y (NPY), pituitary adenylate cyclase-activating peptide (PACAP), and VIP analogs in a superfusion system, and changes in cAMP and IGF-II release from the cells were measured. Various human **cancer** cell lines, such as mammary (MDA-MB-468 and ZR-75-1), prostatic (PC-3), pancreatic (SW-1990 and Capan-2), ovarian (OV-1063), and colorectal (LoVo) responded to pulsatile stimuli with GHRH (0.5-20 nM), VIP (0.02-10 nM), and PACAP-38 (0.05-5 nM) with a rapid, transient increase in cAMP release from the cells. The VIP antagonist, PG-97-269, and the adenylate cyclase inhibitor, MDL-12330A, but not SQ-22536 or pertussis **toxin**, blocked the cAMP responses to these peptides. Stimulation of the cells with 100 nM secretin, glucagon or NPY did not alter the cAMP release. Our results suggest that GHRH receptors different from the type expressed in the pituitary are involved in mediating these effects. As cAMP is a potent second messenger controlling a wide variety of intracellular functions, including those required for cell growth, our results indicate that GHRH might have a direct stimulatory effect on growth of human **cancers**. Blockade of the autocrine/paracrine action of GHRH with its antagonistic analogs may provide a new approach to tumor control.

L39 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2000 ACS
1999:187050 Document No. 130:333094 Luteinizing hormone releasing hormone-RNase A conjugates specifically inhibit the proliferation of LHRH-receptor-positive human prostate and breast tumor cells. Gho, Yong Song; Chae, Chi-Bom (Department of Life Science, Pohang University of Science and Technology, Pohang, 790-784, S. Korea). Mol. Cells, 9(1), 31-36 (English) 1999. CODEN: MOCEEK. ISSN: 1016-8478. Publisher: Springer-Verlag Singapore Pte. Ltd..

AB Human prostate and breast tumor cells produce LH-releasing hormone (LHRH) receptors on their cell surface even when they have lost dependency on sex steroid hormones for growth. To investigate whether LHRH can be used as a cell-binding moiety to deliver **toxin** mols. into prostate and breast tumor cells, LHRH-bovine RNase A conjugates were constructed using the chem. crosslinking method. The treatment of the LHRH receptor-pos. cells such as prostate LNCapFGC and breast MCF7 tumor cells with LHRH-RNase A conjugates resulted in a dose-dependent inhibition of growth. The cytotoxic activities of these conjugates were effectively reduced by the presence of exogenous LHRH. Either free RNase A or LHRH alone did not affect the proliferation of these cells. The LHRH-RNase A conjugates did not show cytotoxicity against FRTL5 and TM4 cells which do not express the LHRH receptors. These results suggest that LHRH can be used as a cell-binding mol. for the specific delivery of **toxin** mols. into the cells which express LHRH receptors on their surface. Thus, a new class of biomedicines that act as fusion proteins between LHRH and **toxins** will give us a new avenue for the treatment of human prostate and breast **cancers**, regardless of their steroid hormone dependency.

L39 ANSWER 5 OF 13 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1998-100377 [09] WPIDS

CR 1990-290154 [38]; 1995-051278 [07]; 1996-105251 [11]; 1996-128611 [13];
1997-288600 [26]; 1998-436609 [37]
AB US 5707964 A UPAB: 19980916
Treating **cancer** where the **cancer** cells have **GnRH** receptors, comprises administering a hormone-**toxin** conjugate in which the hormone is a peptide hormone capable of selectively binding to cells having **GnRH** receptors and the **toxin** is capable of destroying the **cancer** cells.
USE - The treatment is useful especially for treating **cancer** of the breast, prostate or pancreas.
Dwg.0/5

L39 ANSWER 6 OF 13 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1997-288600 [26] WPIDS
CR 1990-290154 [38]; 1995-051278 [07]; 1996-105251 [11]; 1996-128611 [13];
1998-100377 [09]; 1998-436609 [37]
AB US 5631229 A UPAB: 19980916
A method for inactivating gonadotrophs in the pituitary gland of an animal comprises administering a conjugate (I) of a peptide hormone and a **toxin**, where (I) is capable of selectively binding receptors on the gonadotrophs to render them incapable of secreting gonadotropins. The animal is not weakened or killed by the method.
Also claimed is a method for chemically attacking cells with **gonadotropin-releasing hormone** (**GnRH**) receptors comprising administering to an animal an effective amount of a hormone/**toxin** conjugate comprising a peptide hormone capable of binding to **GnRH** receptors.
USE - The methods are for temporarily or permanently sterilising the animal or for treating a sex-hormone-related disease, especially breast **cancer**, prostate **cancer**, pancreatic **cancer** or endometriosis.
Dwg.0/5

L39 ANSWER 7 OF 13 BIOSIS COPYRIGHT 2000 BIOSIS
1997:159310 Document No.: PREV199799458513. G-i protein activation of **gonadotropin-releasing hormone**-mediated protein dephosphorylation in human endometrial carcinoma. Imai, Atsushi (1); Horibe, Shinji; Takagi, Atsushi; Tamaya, Teruhiko. (1) Dep. Obstet. Gynecol., Gifu Univ. Sch. Med., Tsukasamachi, Gifu 500 Japan. American Journal of Obstetrics and Gynecology, (1997) Vol. 176, No. 2, pp. 371-376.
ISSN: 0002-9378. Language: English.
AB OBJECTIVE: **Gonadotropin-releasing hormone** receptor is demonstrated in uterine endometrial carcinomas. This study was performed to determine **gonadotropin-releasing hormone** receptor-mediated membrane events and to identify the guanosine triphosphate binding protein (G protein) subtypes linked to **gonadotropin-releasing hormone** receptor in the tumors. STUDY DESIGN: Endometrial carcinomas surgically removed had been screened for **gonadotropin-releasing hormone** receptor expression before plasma membrane isolation. The phosphoprotein level was observed in the phosphorus 32-labeled incorporation from (gamma-32P)adenosine triphosphate into the isolated plasma membranes. The G-i (alpha subunit) protein was detected by immunoblotting and pertussis **toxin**-catalyzed adenosine diphosphate ribosylation. RESULTS:

Incubation of phosphorus 32-labeled membranes with a **gonadotropin -releasing hormone** analog in the presence of guanosine thiotriphosphate caused a remarkable loss of phosphoprotein from 35 kd protein. This dephosphorylation action was dose dependent of the **gonadotropin-releasing hormone** analog, and the maximal effect (90% loss) occurred at 100 nmol/L. Pertussis **toxin** brought about adenosine diphosphate ribosylation of an immunodetected G-alpha-i. **Gonadotropin-releasing hormone** analog alone or guanosine thiotriphosphate alone had no effect. Pretreatment of the membrane with the pertussis **toxin** completely inhibited **gonadotropin-releasing hormone** -mediated dephosphorylation of the 35 kd protein. CONCLUSION: These data demonstrate the coupling of **gonadotropin-releasing hormone** receptor to protein dephosphorylation through G-i, raising the possibility that the antimitogenic action of **gonadotropin-releasing hormone** may occur by release of the action of protein phosphorylation to promote cell growth.

L39 ANSWER 8 OF 13 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1996-105251 [11] WPIDS
CR 1990-290154 [38]; 1995-051278 [07]; 1996-128611 [13]; 1997-288600 [26];
1998-100377 [09]; 1998-436609 [37]
AB US 5488036 A UPAB: 19980916
Animals are sterilised by admin. of a hormone-**toxin** conjugate that crosses the cell membrane of a gonadotroph and inhibits a gonadotropin release. The conjugate is of the type P-L-T, where P is a peptide hormone that binds to a **GnRH** receptor; L is a linking gp.; and T is a chemical **toxin**, a single-chain **toxin** or a modified **toxin** having an intrinsic toxic gp. but lacking a functional binding domain.

Also claimed are: (A) a method for treating a sex-hormone-related disease selected from breast **cancer**, prostate **cancer**, sex-steroid-dependent tumours, osteoporosis and endometriosis by admin. of a conjugate; (B) a method for inactivating cells whose membranes contain GbRH receptors by admin. of a conjugate of the type P-L-T' (where T' is toxic gp.) to an animal to chemically attack the cells.

ADVANTAGE - Conjugates as above are stated to differ from those described in Biochem. J., 227:1, 343 (1985) in that they contain the membrane translocation domain of the **toxin**.
Dwg.0/5

L39 ANSWER 9 OF 13 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
96274000 EMBASE Document No.: 1996274000. Coupling of **gonadotropin-releasing hormone** receptor to Gi protein in human reproductive tract tumors. Imai A.; Takagi H.; Horibe S.; Fuseya T.; Tamaya T.. Department of Obstetrics/Gynecology, Gifu University School of Medicine, 40 Tsukasamachi,Gifu 500, Japan. Journal of Clinical Endocrinology and Metabolism 81/9 (3249-3253) 1996.
ISSN: 0021-972X. CODEN: JCEMAZ. Pub. Country: United States. Language: English. Summary Language: English.
AB The signaling pathway by which **GnRH** acts in peripheral tumors is distinct from that in the anterior pituitary. We attempted to identify the guanosine triphosphate (GTP)-binding protein (G protein) subtypes linked to **GnRH** receptor in the genital tract tumor membranes. Surgically removed ovarian carcinomas and uterine leiomyosarcomas were screened for **GnRH** receptor expression before plasma membrane isolation. The G.alpha.i was detected by immunoblotting of membrane extracts with specific antibody and pertussis **toxin**-catalyzed

ADP-ribosylation from nicotinamide adenine dinucleotide. Membrane phosphotyrosine phosphatase activity was determined as a **GnRH**-sensitive membrane event using synthetic substrate p-nitrophenyl in a spectrophotometric assay. Pertussis **toxin**, but not cholera **toxin**, brought about ADP-ribosylation of an immunodetected G.alpha.i of 41 kDa in the **GnRH** receptor-positive tumor membrane. Incubation with a **GnRH** analog and GTP decreased the ADP-ribosylation activity in a dose-dependent manner; a half- maximal effect occurred with 30 nmol/L buserelin ($P < 0.01$). The apparent inhibition by **GnRH** of the ADP-ribosylation demonstrated that **GnRH** resolved the .alpha.-subunit of the Gi to GTP-bound form in the membranes. The action of **GnRH** was neutralized by a competitive antagonist, antide. Pretreatment of the membrane with the pertussis **toxin** completely inhibited **GnRH**-sensitive phosphotyrosine phosphatase activity ($P < 0.01$). These data demonstrate the coupling of **GnRH** receptor to Gi protein subfamily. The Gi which couples **GnRH** receptor to the effector may define the difference of responses by peripheral tumor and the anterior pituitary.

L39 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2000 BIOSIS
1996:517984 Document No.: PREV199699240340. Gonadal function of young adults after therapy of malignancies during childhood or adolescence. Mueller, H.
L. (1); Klinkhammer-Schalke, M.; Seelbach-Gobel, B.; Hartmann, A. A.; Kuhl, J.. (1) Julius-Maximilians-Univ., Josef-Schneider-Strasse 2, D-97080
Wuerzburg Germany. European Journal of Pediatrics, (1996) Vol. 155, No. 9,
pp. 763-769. ISSN: 0340-6199. Language: English.
AB As the survival rate of children with malignancies has increased over past
decades, the follow up of adult long-term survivors (LTS) of childhood **cancer** should focus on late effects of disease and treatment. Gonadal function was therefore studied in 54 LTS (aged 17-29 years; 33 male, 21 female) 2-18 years after treatment for malignancies during childhood or adolescence. To analyse the sensitivity of different diagnostic methods, tests of endocrine function (n = 52), spermiograms (n = 14), gynaecological status (n = 20) and ultrasonography of the gonads (n
= 53) were compared with the results of equivalent tests in 23 age-matched
normal controls (12 male, 11 female). There were no differences between male and female LTS concerning age at diagnosis, gonadal dose of irradiation (XRT) and doses of applied chemotherapeutic agents. Where male
LTS had elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) before (P lt 0.05; P lt 0.001) and after (P lt 0.01; P lt 0.001) stimulation with **gonadotropin releasing hormone**, female LTS exhibited normal endocrine function. Accordingly, male patients exhibited lower testicular volumes than normal controls, as measured with a Prader orchidometer (P lt 0.01) or by ultrasonography (P lt 0.001). Gynaecological status and ultrasonography of the gonads were normal in female LTS and controls. Whereas all spermiograms of normal controls (n = 8) showed a normal sperm cell density (SCD), only 2 of 14 male LTS exhibited a normal SCD (P lt 0.001). Azoospermic LTS (n = 9) had been treated more often with alkylating agents and had received higher (P lt 0.05) gonadal doses of XRT. All male LTS with testicular volumes below the normal range (lt 13 ml) and basal FSH levels above the normal range (gt 10 IU/l) exhibited azoospermia, whereas LTS with normal values for testicular volume and basal FSH had a normal SCD. Conclusion: A sex-specific susceptibility for

gonadal damage after treatment for malignancies might be responsible, in part, for the impaired gonadal function of male LTS. Therapy with alkylating agents and/or high gonadal doses of XRT were important risk factors for azoospermia. A simple method to estimate potential fertility in individual LTS is to measure testicular volume, using a Prader orchiometer, and basal FSH serum levels.

L39 ANSWER 11 OF 13 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1995-051278 [07] WPIDS
CR 1990-290154 [38]; 1996-105251 [11]; 1996-128611 [13]; 1997-288600 [26];
1998-100377 [09]; 1998-436609 [37]
AB US 5378688 A UPAB: 19980916
Animals are sterilised by admin. a conjugate (A) of (1) **gonadotropin releasing hormone (GnRH**) or its analogues with (2) one of the **toxins**: ricin; modecoin; abrin; pokeweed antiviral protein (PAP); alpha -amanitin; gelonin; barley, wheat, corn, rye or flax ribosome inhibiting proteins (RIP); diphtheria or shiga **toxins**; Pseudomonas exotoxin; melphalan; methotrexate; N mustards; doxorubicin; daunomycin; or their modified forms. (A) is able to cross the cell membrane of a gonadotroph.

USE - (A), which destroy gonadotropin releasing cells in the pituitary, are used for fertility control (chemical castration) in humans and animals. They can also be used (not claimed) to treat sex hormone related diseases (e.g. breast and prostatic **cancer**; endometriosis) or for reversible suppression of gonadal activity in cases of precocious puberty or during radiation/chemotherapy.

ADVANTAGE - In cattle etc., (A) provide sterilisation without loss of anabolic steroids, so meat quality/prodn. is improved. In humans, sterility is achieved without loss of secondary sexual characteristics. (A) can provide permanent sterility in both males and females without significant toxic effects.
Dwg.0/5

L39 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2000 BIOSIS
1992:370817 Document No.: BA94:52867. STIMULATORY EFFECTS OF FOLLICULAR STIMULATING HORMONE ON THE PROLIFERATION OF OVARIAN **CANCER** CELL LINE IN-VITRO AND IN-VIVO. OHTANI K; SAKAMOTO H; SATOH K. DEP. OBSTET. GYNECOL., NIHON UNIV. SCH. MED., TOKYO, JPN.. ACTA OBSTET GYNAECOL JPN (JPN ED), (1992) 44 (6), 717-724. CODEN: NISFAY. ISSN: 0300-9165.
Language: Japanese.
AB The present study was designed to determine the effects of follicular stimulating hormone (FSH) on the proliferation of the human ovarian **cancer** cell line (HRA line) in vitro and in vivo. The results showed: The number of cells and 3H-thymidine uptake significantly increased after FSH treatment, but were suppressed by Buserelin (number of cells: 2.5 .+-. 0.4 [con] vs 13.8 .+-. 1.7 [FSH] vs 3.0 .+-. 0.2 [FSH + GnRHa] .times. 104/ml, uptake; 1,272.0 .+-. 51.5 [con] vs 4,183.4 .+-. 114.1 [FSH] vs 885.0 .+-. 177.0 [FSH + GnRHa] cpm/105 vaiable cell mean .+-. SD, $p < 0.05$). FSH increased the proportion of the cells in the S phase but decreased the cells in G0/G1 phase (S: 42.1 .+-. 0.72 [con] vs 61.7 .+-. 0.5 [FSH], G0/G1: 53.8 .+-. 0.4 [con] vs 35.5 .+-. 0.6 [FSH]% mean .+-. SD, $p < 0.01$, t-test). Cyclic adenosine monophosphate (cAMP) production by HRA cells was significantly increased by cholera **toxin** (CTX), but not by FSH (1.29 .+-. 0.72 [con] vs 2.05 .+-. 0.21 [FSH] vs 16.2 .+-. 2.28 [CTX] nM mean .+-. SD $p < 0.001$), suggesting

that FSH had no effects on the adenylate cyclase system in the cell line. FSH and GnRHa receptors were identified in HRA cells, and the number of the receptors was significantly decreased by Buserelin treatment (426.0 .+-. 6.8 vs 98.6 .+-. 12.3 sites/cell mean .+-. SD, $p < 0.05$, t-test). When 106 cells were subcutaneously implanted in nude mice, tumors were formed and their size was significantly increased, and survival time was shortened ($p < 0.05$) in animals treated with FSH. The expression of c-myc in HRA cells was increased by FSH. These results suggested that FSH promoted ovarian **cancer** cell growth by increasing the number of cells in the S phase, and the expression of c-myc was correlated with this effect.

L39 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
1991:136750 Document No. 114:136750 Congugates of **gonadotropin-releasing hormone** analogs for destroying gonadotrophs.
Nett, Torrance M.; Glode, L. Michael (Colorado State University Research Foundation, USA). PCT Int. Appl. WO 9009799 A1 19900907, 49 pp.
DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1990-US1038 19900220. PRIORITY: US 1989-314653 19890223.
AB Certain toxic compds. such as, diphtheria **toxin**, ricin **toxin**, Pseudomonas exotoxin, .alpha.-amanitin, pokeweed antiviral protein, ribosome-inhibiting proteins of cereals, gelonin and abrin, as well as certain cytotoxic chems. such as, melphalan and daunorubicin, can be conjugated to analogs of **gonadotropin-releasing hormone GnRH** to form compds. which, when injected into an animal, destroy the gonadotrophs of the anterior pituitary gland. Hence, such compds. may be used to sterilize animals and/or to treat certain sex hormone-related diseases, such as prostate and breast **cancer**. [D-Lys6, des-Gly10]-**GnRH**-ethylamide, synthesized by the solid phase method, was conjugated with pokeweed antiviral protein, using N-succinidinyl 3-(2-pyridyldithio) propionate. Four injections of the conjugate, at 3 day intervals, totally sterilized female rats, and partially male rats.

'IN' IS NOT A VALID FIELD CODE
L40 58 FILE MEDLINE
L41 16 FILE CAPLUS
L42 60 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L43 56 FILE EMBASE
L44 5 FILE WPIDS

TOTAL FOR ALL FILES
L45 195 YARKONI S?/AU,IN

'IN' IS NOT A VALID FIELD CODE
L46 7 FILE MEDLINE
L47 8 FILE CAPLUS
L48 11 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L49 7 FILE EMBASE
L50 5 FILE WPIDS

TOTAL FOR ALL FILES
L51 38 NECHUSHTAN A?/AU,IN

=> s l45 and l51

L52 3 FILE MEDLINE
L53 4 FILE CAPLUS
L54 3 FILE BIOSIS
L55 3 FILE EMBASE
L56 2 FILE WPIDS

TOTAL FOR ALL FILES
L57 15 L45 AND L51

=> s l57 not (l20 or l13 or l32)

L58 1 FILE MEDLINE
L59 1 FILE CAPLUS
L60 1 FILE BIOSIS
L61 1 FILE EMBASE
L62 1 FILE WPIDS

TOTAL FOR ALL FILES
L63 5 L57 NOT (L20 OR L13 OR L32)

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PROCESSING COMPLETED FOR L63
L64 2 DUP REM L63 (3 DUPLICATES REMOVED)

=> d cbib abs 1-2

L64 ANSWER 1 OF 2 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1998-051904 [05] WPIDS
AB WO 9746259 A UPAB: 19980202
Targeted chimeric toxins comprise a cell targeting moiety (consisting of gonadotropin releasing hormone (GnRH)) and a cell killing moiety (consisting of a cell killing toxin) for recognising and destroying specific cells which bear GnRH binding sites.
USE - The chimeric toxins may be used for destroying neoplastic cells, including malignant carcinoma cells, benign uterine lyomyoma cells, endometrial island cells and pituitary tumour adenoma cells. They may be used, e.g. for treatment of uterine myomas, pituitary adenomas, benign prostatic hyperplasia, polycystic breast disease or endometriosis. Administration is, e.g. oral, topical or parenteral (claimed).
Dwg.0/8

L64 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
95071371 Document Number: 95071371. ABL and BCR genes are not imprinted in androgenetic and gynogenetic human tissues. Lorberboum-Galski H; **Yarkoni S; Nechushtan A**; Rachmilewitz J; deGroot N; Hochberg A. (Department of Cellular Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem, Israel..) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1994 Oct 28) 204 (2) 621-7. Journal code: 9Y8. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB In the translocation leading to the formation of the Philadelphia chromosome, the hallmark of chronic myeloid leukemia (CML), the translocated chromosome 9 (ABL), is of paternal descent whereas chromosome

22 (BCR) is of maternal origin (1). To study possible imprinting of the human ABL and BCR genes, we used human tissues exclusively endowed with their maternally (benign teratoma) or paternally (complete hydatidiform mole) inherited chromosomes. Using the sensitive PCR technique followed by northern blotting, we demonstrate here that ABL and BCR are expressed to a similar extent in androgenetic and gynogenetic human tissues, thus suggesting that ABL and BCR genes are not imprinted in these human tissues.

=> s chimer? toxin and target? therap?

L65 4 FILE MEDLINE
L66 4 FILE CAPLUS
L67 3 FILE BIOSIS
L68 4 FILE EMBASE
L69 0 FILE WPIDS

TOTAL FOR ALL FILES
L70 15 CHIMER? TOXIN AND TARGET? THERAP?

=> dup rem l70

PROCESSING COMPLETED FOR L70
L71 5 DUP REM L70 (10 DUPLICATES REMOVED)

=> d cbib abs 1-5

L71 ANSWER 1 OF 5 MEDLINE DUPLICATE 1
1998248937 Document Number: 98248937. [Recombinant immunotoxins and **chimeric toxins** for **targeted therapy** in oncology]. Immunotoxines recombinantes et toxines chim`eres pour une therapie ciblee en oncologie. Chiron M F. (Rhone-Poulenc Rorer Gencell, Centre de recherche de Vitry-Alfortville, France.) BULLETIN DU CANCER, (1997 Dec) 84 (12) 1135-40. Ref: 37. Journal code: BDZ. ISSN: 0007-4551. Pub. country: France. Language: French.
AB Immunotoxins and **chimeric toxins** are hybrid molecules constituted of antibodies, growth factor or cytokines coupled to peptide toxins. They are designed to selectively eliminate tumor cells. Some of these chimera have been shown to induce complete tumor regressions of human tumor xenografts in immunodeficient mice. In clinical trials, higher anti tumor response were observed in lymphoma, brain tumor, breast and colon cancers. Problems arose with normal tissue toxicity and the production of neutralising antibodies. Should the latest recombinant toxins conceived by rationale designed, solved these problems, **chimeric toxins** would be an alternative approach to target tumor cells and vascular endothelial cells in solid tumors.

L71 ANSWER 2 OF 5 MEDLINE DUPLICATE 2
1999035266 Document Number: 99035266. Receptor for interleukin 13 on AIDS-associated Kaposi's sarcoma cells serves as a new target for a potent Pseudomonas exotoxin-based **chimeric toxin** protein.
Husain S R; Obiri N I; Gill P; Zheng T; Pastan I; Debinski W; Puri R K. (Laboratory of Molecular Tumor Biology, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892, USA.) CLINICAL CANCER RESEARCH,

(1997 Feb) 3 (2) 151-6. Journal code: C2H. ISSN: 1078-0432. Pub. country:
United States. Language: English.
AB AIDS-associated Kaposi's sarcoma (AIDS-KS), the most common malignant complication of human immunodeficiency virus infection, is characterized by neoplastic proliferation of mesenchymal cells. AIDS-KS cells release and respond to an array of cytokines through specific plasma membrane receptors. Specific targeting of potent cytotoxic agents to cell surface receptors/antigens on Kaposi's sarcoma cells may provide effective therapy for this malignancy. We have identified a new target in the form of an interleukin 13 (IL-13) receptor that is overexpressed in the five AIDS-KS cell lines examined. Radiolabeled IL-13 cross-linked to a single protein of about Mr 70,000 in AIDS-KS cells. We utilized a chimeric cytotoxic protein composed of IL-13 and a truncated Pseudomonas exotoxin (IL13-PE38QQR), which was found to be specifically and highly cytotoxic to AIDS-KS cells, as determined by protein synthesis inhibition and clonogenic assays. IL13-PE38QQR demonstrated significant antitumor activity in a human epidermoid carcinoma xenograft model. Normal human umbilical vein-derived endothelial, lymphoid, and bone marrow precursor cells expressed low levels of IL-13 receptors, and IL-13 toxin was not cytotoxic to them. Thus, IL-13 receptor on AIDS-KS cells may represent a novel plasma membrane protein(s) that could be utilized to **target therapeutic** agents.

L71 ANSWER 3 OF 5 MEDLINE DUPLICATE 3
96212912 Document Number: 96212912. Generation of active immunotoxins containing recombinant restrictocin. Rathore D; Batra J K. (Immunochemistry Laboratory, National Institute of Immunology, New Delhi, India.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 May 6) 222 (1) 58-63. Journal code: 9Y8. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB Restrictocin, a toxin produced by the fungus Aspergillus restrictus, is a potent inhibitor of eukaryotic protein synthesis. Recombinant restrictocin was made in Escherichia coli and purified to homogeneity in large amounts. The recombinant protein was found to be poorly immunogenic in mice with low toxicity, when injected intraperitoneally. Two immunotoxins were constructed by coupling the recombinant restrictocin to an antibody to the human transferrin receptor, using a cleavable and a stable linkage. The immunotoxins so generated showed specific cytotoxic activity toward receptor bearing cells in tissue culture. Immunotoxin with a cleavable linkage, however, was more active than that containing a stable linkage. Restrictocin appears to be a promising candidate to be developed as a **chimeric toxin** for **targeted therapy**.

L71 ANSWER 4 OF 5 MEDLINE DUPLICATE 4
95348103 Document Number: 95348103. A novel chimeric protein composed of interleukin 13 and Pseudomonas exotoxin is highly cytotoxic to human carcinoma cells expressing receptors for interleukin 13 and interleukin 4.
Debinski W; Obiri N I; Pastan I; Puri R K. (Milton S. Hershey Medical Center, Department of Surgery, Pennsylvania State University, Hershey 17033, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Jul 14) 270 (28) 16775-80. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Chimeric proteins provide a unique opportunity to **target**

therapeutic bacterial toxins to a subset of specific cells. We have generated a new recombinant **chimeric toxin** composed of human interleukin 13 (hIL13) and a Pseudomonas exotoxin A (PE mutant, PE38QQR. The hIL13-PE38QQR chimera is highly cytotoxic to cell lines derived from several human epithelial carcinomas such as adenocarcinoma of stomach, colon, and skin. The cytotoxic action of hIL13-PE38QQR, which can only occur upon internalization of ligand-receptor complex, is blocked by an excess of hIL13 but not of hIL2. This action is not solely hIL13-specific because an excess of hIL4 also blocks the cytotoxicity of hIL13-toxin. Conversely, hIL13 blocks the cytotoxicity of a hIL4-PE38QQR chimera. Binding studies showed that hIL13 displaces competitively 125I-labeled hIL4-PE38QQR on carcinoma cells. These results indicate that IL4 and IL13 compete for a common binding site on the studied human cell lines. Despite this competition, hIL4 but not hIL13 decreased protein synthesis in malignant cells susceptible to the cytotoxicity of both hIL13- and hIL4-PE38QQR. Our results suggest that a spectrum of human carcinomas express binding sites for IL13. Furthermore, hIL13 and hIL4 compete reciprocally for a form of the receptor that is internalized upon binding a ligand. Thus, cancer cells represent an interesting model for studying receptors for these two growth factors. Finally, hIL13-PE38QQR may be a useful agent in the treatment of several malignancies.

L71 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2000 ACS
1996:54619 Document No. 124:109072 Diphtheria toxin-based receptor-specific **chimeric toxins** as **targeted therapies**
Sweeney, Eamonn B.; Murphy, John R. (Evans Memorial Department of Clinical Research, Boston University, Boston, MA, 02118, USA). Essays Biochem., 30, 119-31 (English) 1995. CODEN: ESBIAV. ISSN: 0071-1365.
AB A review and discussion with 23 refs. on **diphtheria toxin**, **Pseudomonas exotoxin** A, ricin toxin, immunotoxins, genetically engineered fusion toxins, and DAB389-IL-7 as a new member of the fusion toxin family.

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